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Editorial

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Cardiovascular prevention at a crossroads: from population-based strategies to precision medicine

La prevención cardiovascular en una encrucijada: de las estrategias poblacionales a la medicina de precisión

Juan José Parcero-Valdés,* Antonio Magaña-Serrano‡

Cardiovascular disease remains the leading cause of mortality worldwide and continues to impose a disproportionate burden in low- and middle-income countries. In Mexico, the convergence of early-onset cardiometabolic disease, a high prevalence of obesity and diabetes, and limited access to preventive strategies has created a scenario in which atherosclerotic cardiovascular disease frequently manifests at younger ages and with greater severity.

For decades, cardiovascular prevention has relied on population-based strategies targeting traditional risk factors. While these approaches have led to meaningful reductions in cardiovascular mortality in high-income countries, their impact has been more limited in regions characterized by early and sustained exposure to cardiometabolic risk.

We are now witnessing a paradigm shift in cardiovascular prevention—one that integrates scalable public health interventions with individualized risk assessment. This dual approach is reflected in the two complementary consensus documents presented in this issue.

The first focuses on cardiovascular immunization, highlighting the role of vaccination —particularly against influenza— as a cost-effective, scalable, and underutilized strategy to reduce cardiovascular events. This approach bridges infectious disease prevention and cardiovascular care, reinforcing the concept that inflammation and infection are integral components of atherothrombotic risk.

The second consensus addresses the integration of polygenic risk scores into cardiovascular risk stratification. By capturing inherited susceptibility from early life, polygenic risk introduces a novel dimension into risk assessment, enabling the identification of individuals whose lifetime risk is not adequately reflected by traditional models.

Together, these two approaches —population-based prevention and precision medicine— should not be viewed as competing paradigms, but rather as complementary strategies within a unified framework of cardiovascular prevention.

In settings such as Mexico, where both high disease burden and resource constraints coexist, the challenge is not only to generate evidence, but also to implement it effectively. Structured initiatives such as the proposed PRS-MX registry represent an important step toward bridging the gap between innovation and real-world clinical practice.

The future of cardiovascular prevention will depend on our ability to integrate early identification of biological risk with scalable interventions that can be applied at the population level. Achieving this balance

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will require collaboration across disciplines, institutions, and healthcare systems.

This supplement reflects a coordinated effort to redefine cardiovascular prevention through the integration of population-based and precision medicine strategies.

On behalf of the AMPAC-ANCAM Multisociety Initiative

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Consensus statement

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Cardiovascular immunization: a multisociety expert consensus on vaccination as a strategy for cardiovascular prevention in high-risk adults in Mexico+

Inmunización cardiovascular: consenso de expertos de múltiples sociedades sobre la vacunación como estrategia para la prevención cardiovascular en adultos de alto riesgo en México

Juan José Parcero-Valdés,* Carlos Zaragoza-Cortes,‡ Carlos Narváez-Oriani,‡ Abel Pavia-López,§ Carlos Ponte-Negretti,¶ Luis Alcocer-Díaz-Barreiro,‖ Salvador Medrano-Ahumada,** Carlos Bazán-Pérez,‡‡ Clemente Zúñiga-Gil,§§ Alexandra Arias,¶¶ Esmeralda Altamirano-Cardoso,*** Carlos Sierra-Fernández,¶¶ Antonio Magaña-Serrano,‡‡‡ Nikos Christo Secchi-Nicolás§§§

Keywords:
Cardiovascular disease, influenza vaccination after myocardial infarction, influenza vaccine to prevent adverse vascular events in heart failure, pneumococcal conjugate vaccine, polysaccharide vaccine.

Palabras clave:
Enfermedad cardiovascular, vacuna contra la influenza después de infarto de miocardio, vacuna contra la influenza para prevenir eventos vasculares adversos en insuficiencia cardiaca, vacuna neumocócica conjugada, vacuna polisacárida.

ABSTRACT

Introduction: acute viral and selected non-respiratory infections, including influenza, SARS-CoV-2, and herpes zoster, are increasingly recognized as important triggers of Major Adverse Cardiovascular Events (MACE), including myocardial infarction, stroke, and heart failure decompensation. Infection-related systemic inflammation, endothelial dysfunction, platelet activation, and prothrombotic responses may destabilize atherosclerotic plaques and precipitate cardiovascular complications. **Objective:** to provide evidence-based recommendations for vaccination strategies in adults with cardiovascular disease as part of comprehensive cardiovascular prevention. The concept of cardiovascular immunization represents an emerging paradigm in preventive cardiology, integrating infection prevention with traditional cardiovascular risk reduction

RESUMEN

Introducción: *las infecciones virales agudas y algunas infecciones no respiratorias, como la gripe, el SARS-CoV-2 y el herpes zóster, se reconocen cada vez más como desencadenantes importantes de eventos cardiovasculares adversos mayores (MACE, por sus siglas en inglés), como el infarto de miocardio, el accidente cerebrovascular y la descompensación de la insuficiencia cardíaca. La inflamación sistémica relacionada con la infección, la disfunción endotelial, la activación plaquetaria y las respuestas protrombóticas pueden desestabilizar las placas ateroscleróticas y precipitar complicaciones cardiovasculares.* ***Objetivo:*** *proporcionar recomendaciones basadas en la evidencia para estrategias de vacunación en adultos con enfermedad cardiovascular como parte de una prevención cardiovascular integral. El concepto de inmunización cardiovascular representa un paradigma*

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strategies. **Material and methods:** this expert consensus was developed by a multidisciplinary panel of specialists in cardiology, internal medicine, infectious diseases, and geriatrics under the auspices of AMPAC and ANCAM. A structured literature review of randomized clinical trials, meta-analyses, observational studies, and international clinical practice guidelines was performed, focusing on vaccines against influenza, pneumococcus, SARS-CoV-2, respiratory syncytial virus, and herpes zoster. **Results:** influenza vaccination has the strongest evidence for cardiovascular protection and is recommended as a class I intervention in patients with cardiovascular disease, supported by randomized clinical trials and meta-analyses demonstrating reductions in cardiovascular mortality and major adverse cardiovascular events.Additional vaccines—including pneumococcal, SARS-CoV-2, respiratory syncytial virus, and herpes zoster—may further reduce infection-related cardiovascular complications, particularly in older adults and high-risk populations.**Conclusions:** vaccination should be considered an essential component of comprehensive cardiovascular prevention strategies in patients with cardiovascular disease. Integrating immunization into routine cardiovascular care may reduce infection-triggered cardiovascular events, hospitalizations, and healthcare burden.

emergente en cardiología preventiva, que integra la prevención de infecciones con las estrategias tradicionales de reducción del riesgo cardiovascular. ***Material y métodos:*** *este consenso de expertos fue desarrollado por un panel multidisciplinario de especialistas en cardiología, medicina interna, enfermedades infecciosas y geriatría bajo los auspicios de AMPAC y ANCAM. Se realizó una revisión estructurada de la literatura de ensayos clínicos aleatorizados, metaanálisis, estudios observacionales y guías de práctica clínica internacionales, centrándose en las vacunas contra la influenza, el neumococo, el SARS-CoV-2, el virus sincitial respiratorio y el herpes zóster.* ***Resultados:*** *la vacunación contra la influenza tiene la evidencia más sólida de protección cardiovascular y se recomienda como una intervención de clase I en pacientes con enfermedad cardiovascular, respaldada por ensayos clínicos aleatorizados y metaanálisis que demuestran reducciones en la mortalidad cardiovascular y eventos cardiovasculares adversos mayores. Las vacunas adicionales, incluidas las neumocócicas, SARS-CoV-2, virus sincitial respiratorio y herpes zóster, pueden reducir aún más las complicaciones cardiovasculares relacionadas con la infección, particularmente en adultos mayores y poblaciones de alto riesgo.* ***Conclusiones:*** *la vacunación debe considerarse un componente esencial de las estrategias integrales de prevención cardiovascular en pacientes con enfermedad cardiovascular. Integrar la inmunización en la atención cardiovascular de rutina puede reducir los eventos cardiovasculares desencadenados por infecciones, las hospitalizaciones y la carga de atención médica.*

Abbreviations:

ACC =American College of Cardiology
AHA =American Heart Association
AMPAC = Mexican Association for the Prevention of Atherosclerosis and its Complications
ANCAM = National Association of Cardiology of Mexico
ANCCMR = National Association of Cardiologists of *Centro Médico La Raza*
ANCISSSTE = National Association of Cardiologists of ISSSTE
CVD = Cardiovascular Disease
ESC = European Society of Cardiology
IAMI = Influenza Vaccination After Myocardial Infarction
IVVE = Influenza Vaccine to Prevent Adverse Vascular Events in Heart Failure
MACE = Major Adverse Cardiovascular Events
PCV20 = Pneumococcal Conjugate Vaccine
PPSV23 = Polysaccharide Vaccine
RSV = Respiratory Syncytial Virus
SIAC = Inter-American Society of Cardiology
SMC = Mexican Society of Cardiology
WHO = World Health Organization

KEY MESSAGES

1. Acute viral and selected non-respiratory infections, including influenza, SARS-CoV-2, and herpes zoster, represent important triggers of cardiovascular events.[1-7]
2. Influenza vaccination has the strongest evidence for cardiovascular protection, reducing cardiovascular mortality and major adverse cardiovascular events.[8-10]
3. Vaccination against pneumococcus, SARS-CoV-2, RSV, and herpes zoster may reduce infection-related cardiovascular complications in high-risk populations.[3,6,7,11-17]
4. Cardiovascular immunization represents an emerging paradigm in preventive cardiology and should be integrated into cardiovascular prevention strategies.[4,5,18-21]

CLINICAL PERSPECTIVES

What is new

1. Several infectious diseases—including respiratory viral infections and herpes zoster—act as triggers of major adverse cardiovascular events.[1-7]
2. Influenza vaccination reduces cardiovascular mortality and major cardiovascular events in randomized trials and meta-analyses.[4,12,13]
3. Vaccination broadens the scope of cardiovascular prevention beyond traditional therapies.

CLINICAL IMPLICATIONS

1. Cardiologists should routinely assess vaccination status in patients with cardiovascular disease.[14,18-21]
2. Hospitalization for acute coronary syndromes or heart failure represents an opportunity to administer vaccines before discharge.[8,19,22]
3. Vaccination should be integrated alongside lipid lowering, blood pressure control, **metabolic control**, antithrombotic therapy, and lifestyle modification.
4. The contemporary cardiologist should actively **recommend, prescribe, and facilitate vaccination** as part of cardiovascular care.

CENTRAL ILLUSTRATION *(Figure 1)*

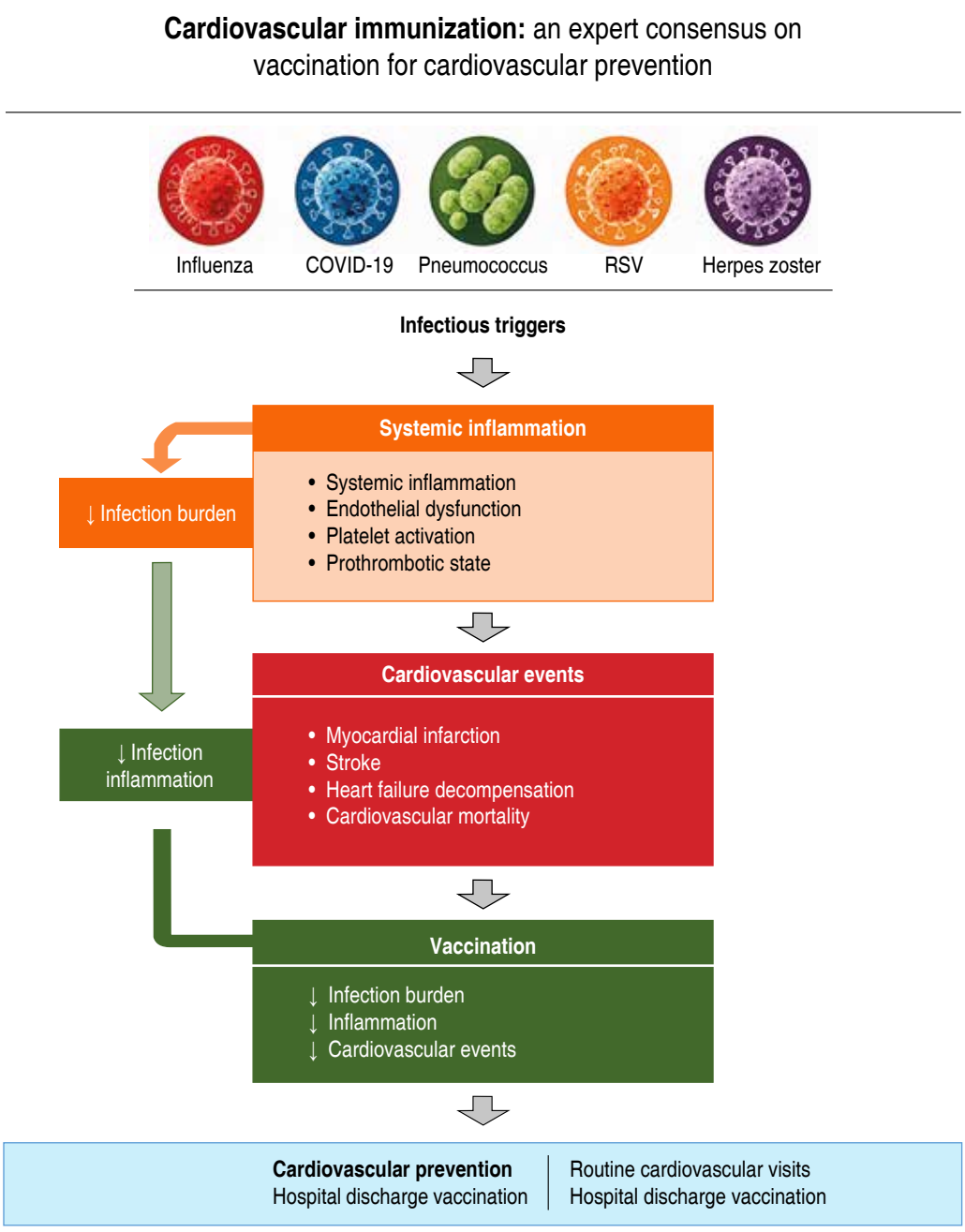

Figure 1: Central illustration. Cardiovascular immunization and cardiovascular prevention.
Infections such as influenza, SARS-CoV-2, pneumococcus, Respiratory Syncytial Virus (RSV), and herpes zoster can trigger cardiovascular events through systemic inflammation, endothelial dysfunction, platelet activation, and prothrombotic states that promote destabilization of atherosclerotic plaques. These mechanisms may precipitate acute cardiovascular complications including myocardial infarction, stroke, and heart failure decompensation. Vaccination against these pathogens reduces infection burden and systemic inflammatory activation and may therefore represent a complementary strategy for cardiovascular prevention in patients with cardiovascular disease.

INTRODUCTION

Cardiovascular Disease (CVD) remains the leading cause of mortality worldwide, accounting for a substantial proportion of global morbidity and healthcare burden.[23] Despite major advances in pharmacologic therapies and preventive strategies, patients with established cardiovascular disease continue to experience high rates of recurrent cardiovascular events.

In recent years, increasing attention has been directed toward the role of infections as triggers of cardiovascular events. Infections—including influenza, SARS-CoV-2, herpes zoster, Respiratory Syncytial Virus (RSV), and bacterial pneumonia—have been associated with increased risks of myocardial infarction, stroke, and heart failure exacerbation.[1,2] Large epidemiological studies have demonstrated strong temporal associations between infections and acute cardiovascular events.

In a landmark study, Kwong and colleagues demonstrated that the risk of acute myocardial infarction increased nearly six-fold during the first week following laboratory-confirmed influenza infection.[2] These findings support the concept that respiratory infections may act as important triggers of cardiovascular events in susceptible individuals.

The mechanisms underlying this association involve several interconnected biological pathways. Acute infections induce systemic inflammatory responses characterized by increased cytokine production, endothelial dysfunction, platelet activation, and a prothrombotic state.[4,5] These mechanisms may destabilize pre-existing atherosclerotic plaques and promote thrombus formation, leading to acute cardiovascular events such as myocardial infarction or ischemic stroke.

In addition to inflammatory activation, acute infections increase metabolic demand and oxygen consumption, potentially precipitating myocardial ischemia in patients with underlying coronary artery disease. Hypoxemia and sympathetic activation during infection may further exacerbate cardiovascular instability.

These observations have led to the concept that preventing infections may represent an additional strategy for reducing cardiovascular risk. Vaccination represents the most effective strategy for preventing many respiratory infections.

By preventing infection-induced inflammation and thrombosis, vaccination may reduce the incidence of infection-triggered cardiovascular events. This paradigm has been referred to as **cardiovascular immunization**, highlighting the emerging role of vaccines as complementary interventions in cardiovascular prevention.[4,5]

The concept of cardiovascular immunization proposes that preventing infections through vaccination may reduce inflammation-mediated cardiovascular complications and improve outcomes in patients with cardiovascular disease.

The mechanisms linking infection, inflammation, and cardiovascular events are summarized in *Table 1*.

Table 1: Mechanisms linking infection and cardiovascular events.

Mechanism	Cardiovascular consequence
Systemic inflammation	Plaque destabilization
Endothelial dysfunction	Impaired vascular regulation
Platelet activation	Increased thrombosis
Prothrombotic state	Acute coronary syndrome or stroke
Hypoxemia	Heart failure decompensation
Immunothrombosis	Increased thrombosis through immunological pathway

Transition to methods. Given the growing recognition of infections as triggers of cardiovascular events and the expanding role of vaccination in adult preventive medicine, this expert consensus was developed to review the available scientific evidence and provide practical recommendations for vaccination strategies in adults with cardiovascular disease.

MATERIAL AND METHODS

Consensus development process

This expert consensus document was developed by a multidisciplinary panel including specialists in cardiology, internal medicine, infectious diseases, and geriatrics under the auspices of the Mexican Association for the Prevention of

Table 2: Major clinical studies evaluating influenza vaccination and cardiovascular outcomes.

Study	Population	Study design	Key findings
IAMI trial	Post-myocardial infarction	Randomized clinical trial	↓ Cardiovascular mortality and ↓ MACE
IVVE trial	Heart failure	Randomized clinical trial	↓ Hospitalizations
PANDA II	Acute heart failure	Cluster randomized trial	↓ Cardiovascular events
Udell et al.	Cardiovascular disease	Meta-analysis	↓ Major cardiovascular events

Atherosclerosis and its Complications (AMPAC), the National Association of Cardiology of Mexico (ANCAM), the Mexican Society of Cardiology (SMC), the National Association of Cardiologists of ISSSTE (ANCISSSTE), and the National Association of Cardiologists of *Centro Médico La Raza* (ANCCMR), with participation of national cardiovascular institutions.

The objective of this document was to review the available scientific evidence linking vaccination to cardiovascular outcomes and to provide practical recommendations for implementing vaccination strategies in adults with cardiovascular disease. This document represents an expert consensus based on available evidence and multidisciplinary discussion, without a formal Delphi process.

A structured literature review was performed in PubMed/MEDLINE, Scopus, and Google Scholar, including studies published between January 2013 and December 2025. Search terms included combinations of: influenza vaccination, pneumococcal vaccination, COVID-19 vaccination, respiratory syncytial virus vaccine, herpes zoster vaccine, cardiovascular disease, myocardial infarction, stroke, heart failure, major adverse cardiovascular events, and prevention.

The literature search included randomized clinical trials, systematic reviews, meta-analyses, observational studies, and international clinical practice guidelines.

Evidence was evaluated for:

1. Influenza
2. Pneumococcal
3. SARS-CoV-2
4. Herpes zoster.
5. RSV

Recommendations were formulated based on available evidence and expert consensus.

RESULTS

Influenza vaccination and cardiovascular prevention

Among currently available vaccines, influenza vaccination has the strongest evidence supporting cardiovascular protection, supported by randomized clinical trials and meta-analyses demonstrating reductions in cardiovascular mortality and major adverse cardiovascular events.[8-10,24-28]

The principal randomized clinical trials and meta-analyses evaluating influenza vaccination and cardiovascular outcomes are summarized in *Table 2*, and the corresponding published effect estimates are visually summarized in *Figure 2*.

Pathophysiological background

Influenza infection has long been associated with increased cardiovascular risk. Viral respiratory infections trigger systemic inflammatory responses characterized by increased cytokine production, endothelial dysfunction, platelet activation, and prothrombotic states.[4,5]

These processes may destabilize atherosclerotic plaques and promote thrombosis, ultimately precipitating acute cardiovascular events such as myocardial infarction or stroke.

Furthermore, infections increase metabolic demand and oxygen consumption, potentially precipitating myocardial ischemia in patients with underlying coronary artery disease.

In patients with heart failure, respiratory infections may exacerbate hemodynamic stress and precipitate decompensation.

Epidemiological evidence

Several epidemiological studies have demonstrated a strong temporal relationship between influenza infection and cardiovascular events.

In a landmark study, Kwong et al. reported that the risk of acute myocardial infarction increased nearly six-fold during the first week following laboratory-confirmed influenza infection.[2]

These findings support the concept that influenza infection may act as a trigger for cardiovascular events in susceptible individuals with underlying atherosclerotic disease.

Randomized clinical trials

IAMI trial

The **Influenza Vaccination After Myocardial Infarction (IAMI) trial** represents one of the most important randomized clinical trials evaluating the cardiovascular benefits of influenza vaccination.[8]

This multicenter randomized trial evaluated influenza vaccination administered shortly after hospitalization for myocardial infarction.

The study demonstrated that influenza vaccination significantly reduced the composite endpoint of:

1. Cardiovascular death.
2. Recurrent myocardial infarction.
3. Stent thrombosis.

Importantly, vaccination was associated with:

1. 28% reduction in major adverse cardiovascular events.
2. 42% reduction in cardiovascular mortality.

These findings provided strong evidence supporting influenza vaccination as a cardioprotective intervention in patients with coronary artery disease.

IVVE trial

The **Influenza Vaccine to Prevent Adverse Vascular Events in Heart Failure (IVVE) trial** evaluated influenza vaccination in patients with symptomatic heart failure.[22]

Although the primary composite outcome of cardiovascular death, myocardial infarction, or stroke did not reach statistical significance, influenza vaccination was associated with reductions in:

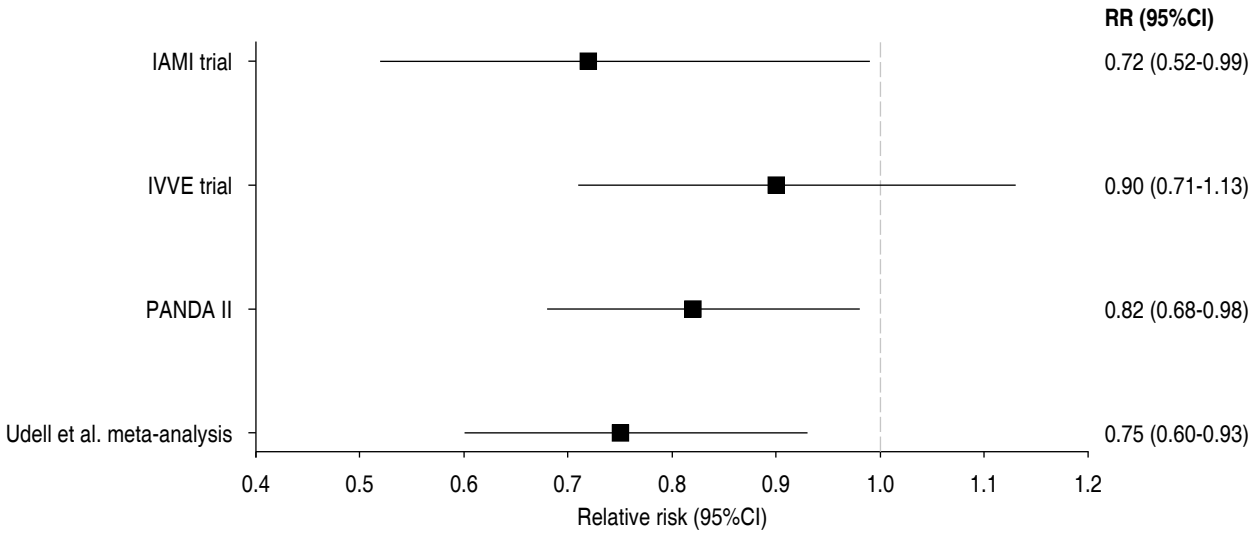

Figure 2: Forest plot of influenza vaccination and cardiovascular outcomes.
Author-generated forest plot based on published effect estimates from the IAMI trial, IVVE trial, PANDA II, and the meta-analysis by Udell et al.[4,5,12,14] Squares represent individual study estimates with horizontal lines indicating 95% confidence intervals. The diamond represents the pooled effect estimate.

1. Hospitalizations.
2. Respiratory complications.

Subgroup analyses suggested greater benefits during periods of high influenza circulation.

PANDA II trial

The **PANDA II trial** evaluated influenza vaccination strategies in patients hospitalized with acute heart failure.[24]

This cluster-randomized trial demonstrated that influenza vaccination was associated with reductions in cardiovascular events and hospitalizations during follow-up.

These findings further support the potential role of influenza vaccination in high-risk cardiovascular populations.

Meta-analyses

Several meta-analyses have evaluated the cardiovascular effects of influenza vaccination.

The meta-analysis conducted by **Udell et al.** demonstrated that influenza vaccination was associated with a significant reduction in major cardiovascular events among patients with established cardiovascular disease.[9]

More recent meta-analyses incorporating randomized trials and observational studies have confirmed reductions in:

1. Cardiovascular mortality.
2. Major adverse cardiovascular events.
3. Hospitalizations.[10,24-28]

In patients with heart failure, pooled analyses have reported reductions in hospitalizations with influenza vaccination, with relative risks of approximately **0.86 (95%CI 0.76-0.97)**.[25-28]

The principal randomized clinical trials and meta-analyses evaluating influenza vaccination and cardiovascular outcomes are summarized in *Table 2*, and the corresponding pooled effects are illustrated in *Figure 2*.

Forest plot summarizing randomized clinical trials and meta-analyses evaluating the association between influenza vaccination and cardiovascular outcomes. The figure illustrates relative risk estimates for major adverse cardiovascular events and cardiovascular mortality among vaccinated individuals with cardiovascular disease. Most studies demonstrate a consistent protective effect of influenza vaccination, particularly in patients with recent myocardial infarction or established coronary artery disease.

Guideline recommendations

The cardiovascular benefits of influenza vaccination are now recognized in major clinical practice guidelines.

The **2023 ACC/AHA guideline for chronic coronary disease** recommends annual influenza vaccination in patients with cardiovascular disease as part of comprehensive preventive care.[18]

Similarly, the **ACC/AHA guideline for acute coronary syndromes** supports influenza vaccination during or shortly after hospitalization for myocardial infarction.[19]

The **European Society of Cardiology (ESC)** also recommends influenza vaccination in patients with cardiovascular disease to reduce infection-triggered cardiovascular events.

Consensus recommendation

Annual influenza vaccination is recommended in all adults with **established cardiovascular disease**, including chronic coronary syndrome, prior myocardial infarction or acute coronary syndrome, heart failure, peripheral arterial disease, atherosclerotic cerebrovascular disease, significant valvular heart disease, and cardiomyopathies.

In adults without established cardiovascular disease but with **high cardiometabolic risk**—including advanced age, diabetes mellitus, obesity, chronic kidney disease, or multiple cardiovascular risk factors—vaccination should follow national immunization schedules and may also confer cardiovascular benefit. Indicated for individuals aged > 6 months. Nasal vaccine not recommended for those > 50 years. Specific recommendations for those > 65 years with inactivated quadrivalent vaccine or high dose.

Class of recommendation: I
Level of evidence: A

Additional vaccines for cardiovascular prevention

Although influenza vaccination has the strongest evidence supporting cardiovascular protection, additional vaccines may contribute to reducing infection-triggered cardiovascular complications in high-risk populations.

These vaccines *(Table 3)* include pneumococcal, SARS-CoV-2, Respiratory Syncytial Virus (RSV), and herpes zoster vaccines, which have demonstrated benefits in preventing severe infections associated with systemic inflammatory responses and cardiovascular complications.[3,6,7,11-17]

Pneumococcal vaccination

Biological rationale

Streptococcus pneumoniae infection remains a major cause of community-acquired pneumonia in adults and is associated with substantial morbidity and mortality. Pneumonia induces systemic inflammatory responses that may increase cardiovascular risk through endothelial dysfunction, activation of coagulation pathways, and plaque destabilization.

Severe pneumococcal infection is characterized by elevated inflammatory mediators, which may promote thrombotic events and contribute to acute coronary syndromes or cerebrovascular events.[12,13]

Additionally, pulmonary infections increase myocardial oxygen demand while impairing oxygen delivery, potentially precipitating myocardial ischemia in patients with pre-existing coronary artery disease.

Epidemiological evidence

Several observational studies have evaluated the association between pneumococcal vaccination and cardiovascular outcomes.

Population-based cohort studies suggest that pneumococcal vaccination may reduce the risk of myocardial infarction and cardiovascular mortality in older adults and individuals with chronic diseases.[12,13]

Although randomized trials specifically designed to evaluate cardiovascular endpoints following pneumococcal vaccination are limited, the biological plausibility and epidemiological evidence support vaccination in high-risk populations.

Guideline context

Current vaccination guidelines recommend pneumococcal vaccination for adults aged ≥ 65

Table 3: Vaccination strategies for cardiovascular prevention.

Vaccine	Target population	Potential cardiovascular impact	Recommendation (class)	Evidence (level)
Influenza	All adults with cardiovascular disease or cardiovascular risk factors	↓ MACE and ↓ cardiovascular mortality	I	A
Pneumococcal	≥ 65 years or high-risk individuals	↓ Infection-triggered cardiovascular events	I	B
SARS-CoV-2	All patients with cardiovascular disease or cardiovascular risk factors	↓ Severe infection and cardiovascular complications	I	B
Herpes zoster	≥ 50 years with cardiovascular disease or cardiovascular risk factors	↓ Infection-related vascular inflammation	I	B
	18-50 years with conditions that could decrease immune capacity	↓ Prevent infection-triggered cardiovascular events		
RSV	≥ 60 years with comorbidities or cardiovascular risk factors	↓ Respiratory infection burden	IIa	B

MACE = Major Adverse Cardiovascular Events. RSV = Respiratory Syncytial Virus.

years and individuals with chronic medical conditions, including cardiovascular disease.[14]

The introduction of newer conjugate vaccines with broader serotype coverage has simplified vaccination schedules and may improve adherence.

Consensus recommendation

Pneumococcal vaccination is recommended in adults ≥ 65 years or those with high cardiovascular risk 18-64 years. In pregnant individuals, vaccination with PCV20 (Pneumococcal Conjugate Vaccine) and PPSV23 (Polysaccharide Vaccine).

Class of recommendation: I
Level of evidence: B

SARS-CoV-2 vaccination

Cardiovascular implications of COVID-19

The COVID-19 pandemic highlighted the strong relationship between viral infections and cardiovascular complications.

SARS-CoV-2 infection has been associated with:

1. Myocardial injury.
2. Myocarditis.
3. Thromboembolic complications.
4. Arrhythmias.
5. Heart failure exacerbation.

Large cohort studies have demonstrated increased risks of myocardial infarction, stroke, and heart failure among individuals infected with SARS-CoV-2 during both the acute phase and long-term follow-up.[3]

Persistent inflammatory and immune-mediated mechanisms may contribute to long-term cardiovascular risk following infection.

Evidence supporting vaccination

Vaccination against SARS-CoV-2 significantly reduces the risk of severe infection, hospitalization, and systemic inflammatory responses.[15]

By preventing severe infection and reducing inflammatory activation, COVID-19 vaccination may indirectly reduce cardiovascular complications associated with infection.

Population studies have demonstrated lower rates of cardiovascular complications among vaccinated individuals compared with unvaccinated individuals following infection.

Consensus recommendation

COVID-19 vaccination with mRNA vaccines is recommended in all patients > 6 months and adults > 65 years with cardiovascular disease or cardiovascular risk factors.

Class of recommendation: I
Level of evidence: B

Respiratory Syncytial Virus (RSV) vaccination

Clinical relevance in older adults

Respiratory syncytial virus infection is increasingly recognized as an important cause of respiratory morbidity in older adults.

RSV infection may lead to severe lower respiratory tract disease and has been associated with increased hospitalization among older individuals with chronic cardiovascular conditions.[16]

Patients with heart failure or chronic cardiopulmonary disease appear particularly vulnerable to RSV-associated complications.

Evidence from clinical trials

Recent phase III clinical trials evaluating RSV vaccines have demonstrated significant reductions in RSV-associated lower respiratory tract disease among adults aged ≥ 60 years.[11]

Although cardiovascular outcomes were not primary endpoints in these trials, preventing severe respiratory infections may reduce cardiovascular stress and prevent decompensation in patients with underlying cardiovascular disease.

Consensus recommendation

RSV vaccination may be considered in adults ≥ 60 years. Recommended options include: RSVPref3 (Arexvy) and Nirsevimab (Beyfortus).

Class of recommendation: IIa
Level of evidence: B

Herpes zoster vaccination

Cardiovascular risk associated with herpes zoster

Herpes zoster infection has been associated with increased risk of stroke and myocardial infarction.

The proposed mechanisms include vascular inflammation, immune-mediated endothelial injury, and systemic inflammatory responses.[6,7]

The risk of stroke appears to be highest during the first weeks following herpes zoster infection but may remain elevated for several months.

Evidence supporting vaccination

The recombinant herpes zoster vaccine demonstrates high efficacy in preventing herpes zoster infection and post-herpetic neuralgia.[17]

Meta-analysis, observational, and case-control studies suggest that vaccination may also reduce cardiovascular risk by preventing infection-associated inflammatory responses that could lead to cardiovascular events.

Consensus recommendation

Herpes zoster vaccination is recommended in adults ≥ 50 years and adults between 18-50 years with increased risk (conditions that could decrease immune capacity) with recombinant zoster vaccine (Shingrix).

Class of recommendation: I
Level of evidence: B

DISCUSSION

The concept of cardiovascular immunization represents a novel approach to cardiovascular prevention, expanding traditional risk reduction strategies beyond pharmacologic and lifestyle interventions to include prevention of infection-triggered cardiovascular events. The growing recognition of infections as triggers of cardiovascular events has important implications for preventive cardiology. The present expert consensus highlights vaccination as an important and often underrecognized strategy for reducing infection-triggered cardiovascular complications in patients with cardiovascular disease.

Evidence for cardiovascular benefit is strongest for influenza vaccination, supported by randomized clinical trials demonstrating reductions in cardiovascular mortality and major adverse cardiovascular events. For other vaccines, available data are derived primarily from meta-analysis and observational studies that reflect the indirect effects related to the prevention of infection-triggered inflammatory responses.

Infection as a trigger of cardiovascular events

A substantial body of epidemiological evidence supports the concept that acute infections may precipitate cardiovascular events in susceptible individuals. Respiratory infections—including influenza, SARS-CoV-2, and bacterial pneumonia—have consistently been associated with increased risks of myocardial infarction, stroke, and heart failure exacerbation.[1-3]

The biological mechanisms underlying these associations involve multiple interconnected pathways. Acute infections induce systemic inflammatory responses characterized by increased levels of pro-inflammatory cytokines and inflammatory mediators. These responses promote endothelial dysfunction and increase platelet reactivity, thereby creating a prothrombotic environment.[4,5]

Systemic inflammation may also destabilize pre-existing atherosclerotic plaques, increasing the likelihood of plaque rupture and thrombus formation. Hypoxemia, increased metabolic demand, and sympathetic activation during acute infections may further contribute to myocardial ischemia and cardiovascular instability.

These mechanisms collectively explain why respiratory infections can act as a «second hit» in patients with underlying cardiovascular disease.

Cardiovascular benefits of vaccination

Among currently available vaccines, influenza vaccination has the most robust evidence

supporting cardiovascular protection. Randomized clinical trials and meta-analyses have consistently demonstrated reductions in cardiovascular events among vaccinated individuals with cardiovascular disease.[8-10,24-28]

The IAMI trial provided strong evidence supporting influenza vaccination as a cardioprotective intervention in patients hospitalized with myocardial infarction.[8] In this study, influenza vaccination administered shortly after hospitalization significantly reduced cardiovascular mortality and recurrent cardiovascular events.

Similarly, the IVVE trial evaluated influenza vaccination in patients with heart failure.[22] Although the primary composite outcome did not reach statistical significance, the trial demonstrated reductions in hospitalizations and respiratory complications among vaccinated patients.

Meta-analyses further support the cardiovascular benefits of influenza vaccination. The meta-analysis conducted by Udell et al. demonstrated a significant reduction in major cardiovascular events among vaccinated patients with cardiovascular disease.[9] More recent analyses incorporating additional randomized trials and observational studies have confirmed reductions in cardiovascular mortality, major adverse cardiovascular events, and hospitalizations.[10,24-28]

These findings support influenza vaccination as an effective strategy for reducing infection-triggered cardiovascular complications.

Expanding the concept of cardiovascular immunization

Although influenza vaccination currently has the strongest evidence base, other vaccines may also contribute to reducing cardiovascular risk, primarily through prevention of infection-triggered inflammatory and thrombotic pathways.

Pneumococcal vaccination may reduce cardiovascular events by preventing severe bacterial pneumonia and the associated inflammatory cascade. Observational studies have suggested protective associations between pneumococcal vaccination and cardiovascular outcomes in older adults.[12,13]

Similarly, vaccination against SARS-CoV-2 reduces the risk of severe infection and systemic inflammatory responses associated with COVID-19.[15] Given the substantial cardiovascular burden associated with COVID-19 infection, vaccination may indirectly reduce cardiovascular complications by preventing severe disease.

Herpes zoster infection has also been associated with increased risk of stroke and myocardial infarction.[6,7] Preventing herpes zoster infection through vaccination may therefore reduce infection-related vascular inflammation.

New vaccines targeting Respiratory Syncytial Virus (RSV) represent another important development in adult vaccination. RSV infection can cause severe respiratory illness in older adults and has been associated with exacerbations of heart failure and other cardiovascular conditions.[11,16]

These observations collectively support the concept of cardiovascular immunization, which integrates infection prevention into cardiovascular risk reduction strategies.

Integration into cardiovascular guidelines

The growing recognition of vaccination as a cardiovascular preventive strategy is reflected in contemporary clinical practice guidelines and international consensus statements.

The American College of Cardiology and American Heart Association (ACC/AHA) recommend annual influenza vaccination for patients with cardiovascular disease as part of comprehensive preventive care.[18,19] Similarly, the European Society of Cardiology (ESC) emphasizes vaccination as a strategy to reduce infection-triggered cardiovascular events.

In the Americas, the Inter-American Society of Cardiology (SIAC) and the World Heart Federation have issued a consensus supporting influenza vaccination as a cardiovascular preventive strategy, reinforcing its relevance in Latin American clinical practice.[20]

In parallel, the World Health Organization (WHO) recommends annual influenza vaccination for high-risk populations, including older adults and individuals with chronic medical conditions, highlighting its importance

from both cardiovascular and public health perspectives.[21]

These recommendations highlight the increasing recognition of vaccination as an integral component of preventive cardiology.

Clinical implications

From a clinical perspective, cardiologists are uniquely positioned to promote vaccination among patients with cardiovascular disease.

Routine cardiovascular visits provide an opportunity to assess vaccination status and ensure that patients receive recommended vaccines. Hospitalization for acute coronary syndromes or heart failure represents another critical opportunity to administer vaccines before discharge.

Integrating vaccination into cardiovascular care pathways may represent a practical, scalable, and cost-effective strategy for reducing infection-related cardiovascular events and improving clinical outcomes.

Public health implications

Increasing vaccination coverage among patients with cardiovascular disease may have important public health implications.

Patients with cardiovascular disease represent a high-risk population for both infectious complications and cardiovascular events. Improving vaccination coverage in this population may reduce hospitalizations, healthcare costs, and mortality.

In regions with high cardiometabolic disease burden, vaccination strategies may represent a scalable intervention for reducing infection-triggered cardiovascular complications. These findings are particularly relevant in low- and middle-income countries, where cost-effective preventive strategies are critically needed.

Limitations

Although the evidence supporting influenza vaccination as a cardioprotective intervention is strong, evidence for other vaccines remains less robust in terms of randomized controlled trials with respect to cardiovascular outcomes.

Most studies evaluating pneumococcal, RSV, or herpes zoster vaccines were not specifically designed to assess cardiovascular endpoints. Therefore, the magnitude of cardiovascular protection associated with these vaccines remains less well defined.

Future randomized clinical trials specifically designed to evaluate cardiovascular outcomes following vaccination would help clarify the magnitude of cardiovascular benefits associated with these vaccines.

Future directions

Future research should focus on evaluating vaccination strategies in high-risk cardiovascular populations through randomized clinical trials designed to assess cardiovascular outcomes.

Advances in immunology and vaccine technology may further expand the role of vaccination in preventive cardiology. In addition, improving vaccination uptake through integrated healthcare strategies represents an important area for future investigation.

These findings are particularly relevant in regions with a high burden of cardiometabolic disease, where scalable and cost-effective preventive strategies such as vaccination may have substantial impact.

Clinical impact across diverse healthcare settings and patient populations. The incorporation of vaccination into routine cardiovascular care pathways may contribute to reducing the burden of cardiovascular events and healthcare utilization in high-risk conditions, highlighting its importance from both cardiovascular and public health perspectives.[21]

These recommendations highlight the increasing recognition of vaccination as an integral component of preventive cardiology.

CONCLUSIONS

Vaccination represents an important and often underrecognized strategy for cardiovascular prevention. Preventing infections that trigger systemic inflammation may reduce cardiovascular events and improve outcomes in patients with cardiovascular disease. Integrating immunization into routine cardiovascular care should

therefore be considered part of comprehensive cardiovascular prevention strategies. The concept of cardiovascular immunization highlights the emerging role of vaccines as complementary interventions alongside traditional therapies for cardiovascular risk reduction.

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CONSENSUS STATEMENT

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Multisociety Mexican Consensus on the integration of polygenic risk in cardiovascular risk stratification: implications for precision cardiovascular medicine in Mexico+

Consenso multisocietario mexicano sobre la integración del riesgo poligénico en la estratificación del riesgo cardiovascular: implicaciones para la medicina cardiovascular de precisión en México

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Keywords: Polygenic risk score, coronary artery calcium, mexican polygenic risk registry.

Palabras clave: *Puntuación de riesgo poligénico, calcio en las arterias coronarias, registro mexicano de riesgo poligénico.*

ABSTRACT

Introduction: cardiovascular disease remains the leading cause of mortality in Mexico, accounting for approximately one in four deaths nationwide. The epidemiological transition is characterized by a high prevalence of obesity, type 2 diabetes mellitus, hypertension, and atherogenic dyslipidemia from early stages of life, resulting in prolonged cumulative cardiometabolic exposure and earlier onset of atherosclerotic events. Traditional risk models, based on phenotypic variables and strongly dependent on chronological age, tend to underestimate biological susceptibility in younger individuals. **Objective:** to establish a multisociety position on the clinical use of Polygenic Risk Scores (PRS) in Mexico and to define a national implementation strategy linked to real-world evidence generation through the PRS-MX Registry. **Material and methods:** this consensus document was developed through a structured literature review and a modified Delphi methodology involving national experts in clinical cardiology, interventional cardiology, lipidology, genetics, and public health. **Results:** PRS is independent of traditional risk factors, improves risk reclassification in primary prevention, and identifies individuals with greater absolute benefit

RESUMEN

Introducción: *las enfermedades cardiovasculares siguen siendo la principal causa de mortalidad en México, ya que representan aproximadamente una de cada cuatro muertes en todo el país. La transición epidemiológica se caracteriza por una elevada prevalencia de obesidad, diabetes mellitus tipo 2, hipertensión y dislipidemia aterogénica desde las primeras etapas de la vida, lo que da lugar a una exposición cardiometabólica acumulada prolongada y a una aparición más temprana de eventos ateroscleróticos. Los modelos de riesgo tradicionales, basados en variables fenotípicas y fuertemente dependientes de la edad cronológica, tienden a subestimar la susceptibilidad biológica en individuos más jóvenes.* ***Objetivo:*** *establecer una postura conjunta de varias sociedades sobre el uso clínico de las puntuaciones de riesgo poligénico (PRS) en México y definir una estrategia nacional de implementación vinculada a la generación de evidencia del mundo real a través del Registro PRS-MX.* ***Material y métodos:*** *este documento de consenso se elaboró mediante una revisión de la literatura estructurada y una metodología Delphi modificada, en la que participaron expertos nacionales en cardiología clínica, cardiología intervencionista,*

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from lipid-lowering therapies. A three-dimensional model integrating phenotype, anatomy, and genotype is proposed. **Conclusions:** selective implementation of PRS in Mexico represents a step toward precision cardiovascular medicine and should be carried out in a stepwise manner linked to national evidence generation.

lipidología, genética y salud pública. ***Resultados:*** *el PRS es independiente de los factores de riesgo tradicionales, mejora la reclasificación del riesgo en la prevención primaria e identifica a las personas que obtienen un mayor beneficio absoluto de los tratamientos hipolipemiantes. Se propone un modelo tridimensional que integra el fenotipo, la anatomía y el genotipo.* ***Conclusiones:*** *la implementación selectiva de la PRS en México supone un paso hacia la medicina cardiovascular de precisión y debería llevarse a cabo de forma gradual, ligada a la generación de evidencia a nivel nacional.*

Abbreviations:
PRS = Polygenic Risk Score
CAC = Coronary Artery Calcium
LDL-C = Low-Density Lipoprotein Cholesterol
Lp(a) = Lipoprotein(a)
PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9
ESC = European Society of Cardiology
PRS-MX = Mexican Polygenic Risk Registry

KEY MESSAGES

What is new?

1. This is the first multisociety consensus addressing the clinical integration of polygenic risk in cardiovascular prevention in Mexico.
2. Polygenic Risk Scores (PRS) redefine cardiovascular risk as a lifelong trajectory, rather than a short-term probability.
3. A novel three-dimensional model integrating phenotype, anatomy (Coronary Artery Calcium CAC), and genotype (PRS) is proposed as a framework for precision cardiovascular risk stratification.

What are the clinical implications?

1. PRS enables early identification of individuals with accelerated atherosclerotic trajectories, particularly in young adults and those at intermediate risk.
2. The integration of PRS with CAC and traditional risk factors improves clinical decision-making in primary prevention.
3. Implementation should be selective and evidence-based, linked to national validation through the PRS-MX Registry.
4. Precision cardiovascular prevention strategies may optimize resource allocation by targeting individuals with the greatest expected benefit.

INTRODUCTION

Cardiovascular disease remains the leading cause of mortality in Mexico, accounting for approximately one quarter of all registered deaths nationwide.[1] This occurs in the context of an epidemiological transition characterized by a high prevalence of obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease, and atherogenic dyslipidemia beginning early in life.[2-5] The pathophysiological consequence is prolonged cumulative exposure to apolipoprotein B-containing lipoproteins, low-grade systemic inflammation, and endothelial dysfunction, leading to the development of subclinical atherosclerosis decades before clinical manifestation.

Contemporary risk prediction models have substantially improved cardiovascular prevention by integrating variables such as age, sex, blood pressure, lipid profile, smoking status, and diabetes into validated multivariable equations.[6,7] However, these models are predominantly phenotypic and rely heavily on chronological age as a determinant of risk. In populations with early cardiometabolic exposure, such as the Mexican population, this temporal dependence results in systematic underestimation of true biological susceptibility.

Evidence from Mendelian randomization studies has demonstrated that cumulative lifetime exposure to Low-Density Lipoprotein Cholesterol (LDL-C) is a central determinant of atherosclerotic cardiovascular disease risk, and that modest but sustained reductions from early life are associated with substantially greater reductions in cardiovascular risk than intensive reductions initiated later.[8-11] This paradigm underscores the need for tools capable of identifying risk trajectories from birth.

Polygenic Risk Scores (PRS) quantify this biological susceptibility through the weighted integration of multiple common genetic variants associated with coronary artery disease.[12-15] Their incorporation into clinical practice represents a transition toward precision cardiovascular medicine.

CONSENSUS METHODOLOGY

This document was developed by the Working Group on Cardiovascular Prevention and Precision Medicine of the Mexican Association for the Prevention of Atherosclerosis and its Complications (AMPAC for its abbreviation in spanish), in collaboration with the National Association of Cardiologists of Mexico (ANCAM for its abbreviation in spanish), the Mexican Society of Cardiology (SMC for its abbreviation in spanish), the National Association of Cardiologists of ISSSTE (ANCISSSTE for its abbreviation in spanish), and the National Association of Cardiologists of Centro Médico La Raza (ANCCMR for its abbreviation in Spanish).

A structured literature review was conducted using PubMed, EMBASE, and the Cochrane Library from January 2005 to December 2025. The review included genome-wide association studies, meta-analyses of polygenic risk scores, clinical validation studies, risk reclassification analyses, and subanalyses of lipid-lowering clinical trials.

Evidence appraisal incorporated discrimination, calibration, net reclassification improvement, integrated discrimination improvement, and absolute risk reduction.

Relevant international guidelines, particularly those from the European Society of Cardiology and North American cardiovascular societies, were reviewed.[6,7,16-18] Recommendations were developed through expert consensus and categorized according to classes of recommendation and levels of evidence based on the European Society of Cardiology framework.

The final content was reviewed and approved by all members of the AMPAC–ANCAM–SMC–ANCISSSTE–ANCCMR consensus group, ensuring applicability within the Mexican healthcare system.

THREE-DIMENSIONAL MODEL OF CARDIOVASCULAR RISK STRATIFICATION

The integration of PRS into clinical practice *(Figure 1)* should not be interpreted as a replacement of existing risk assessment tools, but rather as the incorporation of a third dimension into cardiovascular risk stratification.

Traditionally, risk estimation has relied on phenotypic variables that reflect the patient's current clinical status and allow estimation of short- and intermediate-term event probability.

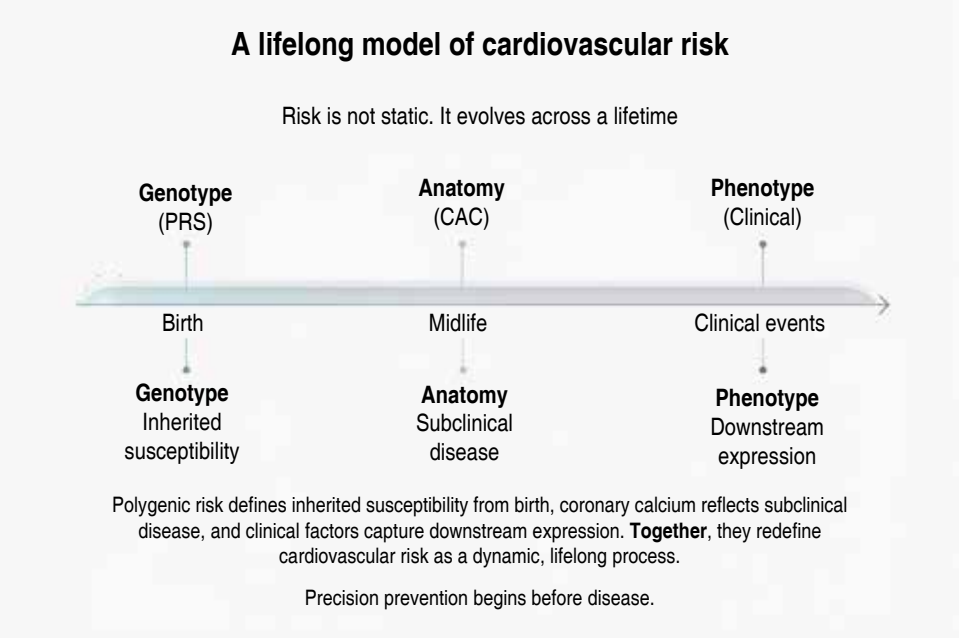

Figure 1:

Three-dimensional model of cardiovascular risk stratification: phenotype, anatomy, and genotype. A conceptual framework integrating phenotypic risk factors, anatomical burden of subclinical atherosclerosis assessed by coronary artery calcium, and genetic susceptibility captured by polygenic risk scores (PRS). Together, these dimensions redefine cardiovascular risk as a **dynamic, lifelong trajectory**, enabling a more precise and individualized approach to risk stratification. CAC = Coronary Artery Calcium. PRS = Polygenic Risk Scores.

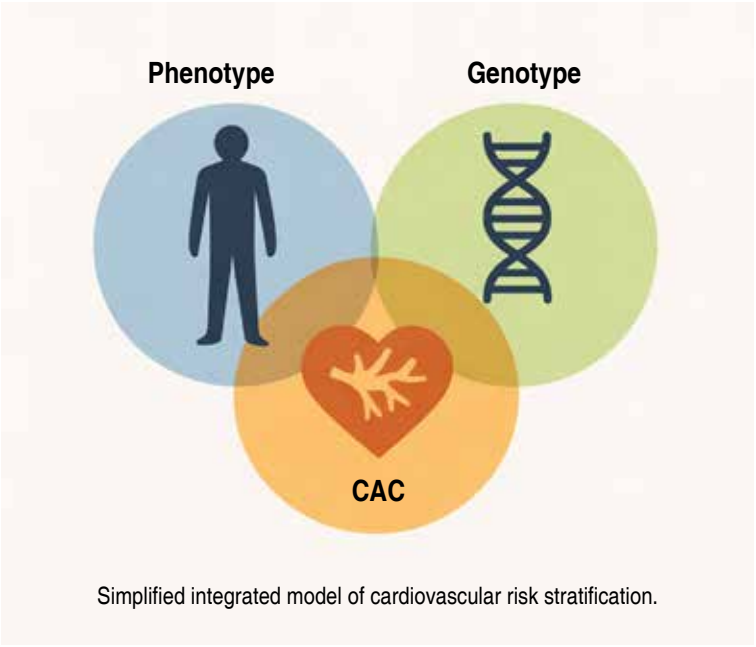

Figure 2: Simplified integrated model of cardiovascular risk stratification. CAC = Coronary Artery Calcium.

The introduction of Coronary Artery Calcium (CAC) scoring added an anatomical dimension, enabling the detection of established subclinical atherosclerosis. PRS introduces a genotypic dimension that captures inherited susceptibility and enables estimation of the biological risk trajectory from birth.

Together, these three domains (phenotype, anatomy, and genotype) form a unified, multidimensional framework for cardiovascular risk assessment,[6,12,19] as illustrated in *Figure 2*.

This model addresses three fundamental clinical questions: what is the patient's current risk, whether subclinical atherosclerotic disease is already present, and what is the expected trajectory of disease progression over time.

From a temporal perspective, PRS operates upstream, CAC reflects an intermediate stage of disease, and phenotypic models capture downstream clinical expression. This sequential framework explains why PRS has its greatest clinical impact early in life, whereas CAC becomes more informative in midlife.

The integration of these dimensions enables a dynamic and individualized approach to risk stratification and represents a conceptual foundation for precision cardiovascular medicine.

Schematic representation of the interaction between phenotype, genotype, and coronary artery calcium (CAC) as complementary components of cardiovascular risk assessment. The overlap illustrates the integrated nature of

biological susceptibility, subclinical disease, and clinical expression within a unified precision medicine framework. This model addresses three fundamental clinical questions: what is the patient's current risk, whether subclinical atherosclerotic disease is already present, and what is the expected trajectory of disease progression over time.

From a temporal perspective, PRS operates upstream, CAC reflects an intermediate stage of disease, and phenotypic models capture downstream clinical expression. This sequential framework explains why PRS has its greatest clinical impact early in life, whereas CAC becomes more informative in midlife.

The integration of these dimensions enables a dynamic and individualized approach to risk stratification and represents a conceptual foundation for precision cardiovascular medicine.

PRS, CORONARY ARTERY CALCIUM, AND LIPOPROTEIN(A): COMPLEMENTARY TOOLS

Coronary artery calcium scoring has consistently demonstrated its ability to refine cardiovascular risk stratification in primary prevention, particularly among individuals classified as having intermediate risk.[19,20] A CAC score of zero is associated with very low short-term risk, whereas higher values identify individuals with substantially increased risk.

However, CAC reflects established disease rather than underlying biological susceptibility. In younger individuals with high genetic risk, the absence of calcification does not exclude an active atherosclerotic process.

Table 1: Integrated framework combining polygenic risk score, coronary artery calcium, and lipoprotein(a) for cardiovascular risk stratification.

Tool	What it captures	Biological timing
PRS	Genetic susceptibility	Lifelong (from birth)
CAC	Subclinical atherosclerosis	Intermediate stage
Lp(a)	Inherited thrombogenic risk	Constant

CAC = Coronary Artery Calcium. Lp(a) = lipoprotein(a). PRS = Polygenic Risk Score.

In this context, PRS provides a measure of inherited susceptibility and enables identification of accelerated risk trajectories decades before the development of detectable calcification.

Lipoprotein(a) [Lp(a)] is a genetically determined, causal, and independent risk factor for atherosclerotic cardiovascular disease, as supported by genetic and epidemiological evidence.[21] Unlike PRS, which integrates multiple biological pathways, Lp(a) reflects a specific proatherogenic and prothrombotic mechanism.

The combined assessment of PRS, CAC, and Lp(a) allows a comprehensive characterization of cardiovascular risk by integrating biological susceptibility, disease burden, and thrombogenic potential *(Table 1)*.

HIGH-IMPACT CLINICAL SCENARIOS IN MEXICO

The clinical value of PRS is greatest in scenarios where discordance exists between estimated risk based on traditional models and clinical judgment *(Table 2)*.

In young adults with a family history of premature coronary artery disease, chronological age significantly lowers calculated risk in conventional algorithms. This often leads to delayed implementation of preventive strategies despite the presence of adverse metabolic profiles. PRS enables the identification of individuals with accelerated atherosclerotic trajectories who may benefit from earlier intervention.[10,13,22]

Individuals classified as having intermediate risk represent the primary zone of therapeutic uncertainty in primary prevention. The incorporation of PRS allows reclassification toward higher or lower biological risk, optimizing clinical decision-making and resource allocation.[11,15,23,24]

In women undergoing menopausal transition, PRS may help differentiate between metabolic changes related to aging and underlying biological susceptibility, facilitating more individualized prevention strategies.

In early cardiorenal–metabolic syndrome (characterized by central obesity, hypertriglyceridemia, reduced HDL-C, and insulin resistance) PRS enables identification of high-risk phenotypes with accelerated disease progression.

Table 2: Clinical scenarios in which polygenic risk score may modify decision-making in primary prevention.

Recommendation	Class	Level
Use of PRS in young adults with family history of premature coronary artery disease	IIa	B
Use of PRS in individuals with intermediate risk and therapeutic uncertainty	IIa	B
Use of PRS to support intensification of lipid-lowering strategies in primary prevention	IIb	B
PRS should not be used as a standalone decision-making tool	III	C
Validation of PRS in the Mexican population prior to widespread implementation	I	C

PRS = Polygenic Risk Score.
Classification of recommendations and levels of evidence adapted from the European Society of Cardiology (ESC) Guidelines.[6,7,16]

Table 3: Classes of recommendation and levels of evidence.

Class	Definition
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the treatment or procedure is not useful/effective and in some cases may be harmful
Level	**Source of evidence**
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of expert opinion and/or small studies, retrospective studies, registries

Classification of recommendations and levels of evidence adapted from the European Society of Cardiology (ESC) Guidelines.[6,7,16]

CONSENSUS RECOMMENDATIONS

Recommendations are categorized according to classes of recommendation and levels of evidence, as defined in *Table 3*.

THERAPEUTIC IMPLICATIONS AND ABSOLUTE RISK REDUCTION

Contemporary guidelines recommend tailoring lipid-lowering therapy according to global cardiovascular risk.[21,25] In this context, PRS introduces an additional dimension by identifying individuals who are more biologically susceptible and, consequently, who have a greater potential for absolute benefit from intervention.

Evidence derived from clinical trial subanalyses has demonstrated that individuals with higher polygenic risk derive the greatest absolute reduction in cardiovascular events with statin therapy, despite achieving similar reductions in LDL-C levels.[11] This finding supports a precision medicine approach in

which treatment intensity is aligned with underlying biological risk rather than solely phenotypic profiles.

Similarly, in the FOURIER and ODYSSEY OUTCOMES trials, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors provided the greatest benefit to individuals with higher baseline risk. Notably, risk reduction did not reach statistical significance in individuals with low or intermediate polygenic risk, reinforcing the concept of allocating high-cost therapies to those with the highest expected benefit.[26,27]

From a clinical perspective, PRS should be interpreted as a modifier of risk that refines therapeutic decision-making, rather than as an isolated determinant.

IMPACT ON INTERVENTIONAL CARDIOLOGY

Interventional cardiology in Mexico faces a high burden of complex atherosclerotic disease in relatively young patients. Early identification of individuals with accelerated risk trajectories has the potential to reduce the incidence of premature multivessel disease, decrease the need for complex revascularization procedures, and modify the epidemiological profile of coronary artery disease.

From this perspective, PRS is not only a primary prevention tool but also a strategy with long-term implications for interventional cardiology practice.

HEALTH ECONOMICS AND RESOURCE ALLOCATION

The incorporation of genomic tools into healthcare systems with constrained resources requires evaluation not only of diagnostic performance but also of cost-effectiveness and resource allocation.

In middle-income countries, preventive strategies that target individuals at the highest absolute risk have been the most effective at reducing cardiovascular events.[28,29] By identifying individuals with accelerated risk trajectories early in life, PRS enables more targeted and intensive interventions in selected populations.

This approach is particularly relevant in Mexico, where premature cardiovascular disease imposes a substantial burden in terms of disability-adjusted life years and indirect costs related to loss of productivity.

From this perspective, PRS should be considered not merely as a diagnostic tool, but as a stratification instrument capable of optimizing the allocation of high-cost therapies—such as PCSK9 inhibitors, ezetimibe, or combination lipid-lowering strategies—to individuals with the greatest expected clinical benefit.[26-29]

MEXICAN POLYGENIC RISK REGISTRY (PRS-MX)

The clinical implementation of PRS in Mexico must be closely linked to the generation of national evidence through the PRS-MX Registry, designed as a prospective, multicenter, real-world cohort.

The initial enrollment phase will extend through the third quarter of 2026, with potential extension depending on recruitment dynamics. The primary objective is to evaluate the impact of PRS on therapeutic decision-making in primary prevention.

Secondary objectives include assessment of LDL-C target achievement, intensification of lipid-lowering therapy, treatment adherence, and incidence of cardiovascular events during follow-up.

The registry will systematically collect demographic variables, traditional risk factors, biochemical parameters, treatment strategies, therapeutic targets, and clinical outcomes. This design will enable evaluation of the real-world effectiveness of PRS and support calibration of predictive models in the Mexican population.

Its collaborative structure will allow broad national participation and ensure recognition of contributing investigators in subsequent publications.

CUMULATIVE EXPOSURE TO APOB-CONTAINING LIPOPROTEINS: A UNIFYING PARADIGM

The concept of cumulative exposure to atherogenic lipoproteins provides the pathophysiological link between genetic susceptibility and clinical expression of coronary artery disease.

Mendelian randomization studies have demonstrated that sustained reductions in LDL-C from early life are associated with substantially greater reductions in cardiovascular risk compared with intensive reductions initiated later.[8-11,30] This time-dependent effect reflects the cumulative nature of atherosclerosis.

Importantly, the relationship between LDL-C levels and cardiovascular risk is modulated by polygenic background, resulting in heterogeneous risk trajectories among individuals with similar lipid profiles.[31-33]

PRS enables estimation of the expected rate of cumulative atherogenic exposure and, therefore, the lifelong trajectory of cardiovascular risk.

In populations characterized by early cardiometabolic exposure, such as Mexico, this paradigm highlights the limitations of age-based intervention thresholds and supports earlier, biology-driven prevention strategies.

PERFORMANCE OF PRS IN MULTIETHNIC POPULATIONS

The Mexican population presents a complex genetic architecture derived from admixture of Amerindian, European, and African ancestries, with significant regional variation.[34]

This multiethnic background has direct implications for the transferability of PRS developed in predominantly European populations. Recent studies have demonstrated that PRS retain their ability to stratify risk in non-European populations when adjusted for ancestry and recalibrated using local data, although with a modest reduction in discriminatory performance.[35-37]

This limitation does not represent a barrier, but rather a strong rationale for the generation of national evidence.

The PRS-MX Registry will enable evaluation of PRS performance in the Mexican population, development of locally calibrated models, and exploration of the interaction between genetic susceptibility and cardiometabolic exposure.

COMMUNICATION OF GENETIC RISK AND BEHAVIORAL CHANGE

Effective communication of genetic risk is a critical component of PRS implementation. Available evidence demonstrates that structured communication of genetic risk, framed within a modifiable risk model, does not induce biological determinism or significant anxiety. On the contrary, it improves adherence to lipid-lowering therapy and promotes sustained lifestyle changes.[38-40]

Clinical communication should emphasize the concept of a modifiable risk trajectory and the benefits of early intervention.

IMPLEMENTATION SCIENCE AND HEALTH SYSTEM INTEGRATION

The adoption of diagnostic innovations depends not only on scientific evidence but also on structured implementation pathways. Implementation science has demonstrated that successful integration requires progressive phases including academic validation, process standardization, clinician education, and evaluation of clinical and economic impact.[41]

In Mexico, PRS implementation should follow a stepwise model:

Phase 1: Controlled academic implementation in specialized centers

Phase 2: National validation through the PRS-MX Registry

Phase 3: Selective integration into broader cardiometabolic care networks

This structured approach prevents indiscriminate adoption and ensures evidence-based implementation.

ETHICAL AND LEGAL CONSIDERATIONS

The clinical use of genetic information requires a robust ethical and legal framework.

Informed consent must include clear explanation of the probabilistic nature of PRS, its limitations, and its complementary role relative to traditional risk assessment tools.

Genetic data must be protected according to national regulations and international standards of confidentiality and data security. Mechanisms should also be established to prevent discrimination based on genetic information in employment or insurance contexts.

PRS should be used exclusively within clinical and research settings and not for non-medical population screening purposes.

EVIDENCE GAPS

Despite rapid advances in cardiovascular genomics, important gaps remain. The absence of randomized clinical trials specifically designed to evaluate PRS-guided therapeutic strategies represents the main limitation.

Most available evidence derives from observational studies and post hoc analyses. Additional research is required to define intervention thresholds based on genetic risk percentiles and to integrate PRS into existing treatment algorithms.

Further areas of interest include its role in secondary prevention, residual risk assessment, and integration with imaging modalities such as coronary artery calcium in cost-effectiveness models.

NATIONAL RESEARCH AGENDA (2026-2030)

This consensus establishes a national research agenda focused on:

1. Development of PRS calibrated for the Mexican population
2. Evaluation in early cardiorenal–metabolic syndrome
3. Impact on treatment intensification and LDL-C target achievement
4. Integration with imaging tools in cost-effectiveness models
5. Role in secondary prevention and residual risk

This agenda aims to position Mexico as a regional leader in precision cardiovascular medicine.

LATIN AMERICAN PROJECTION

The development of a multisociety consensus and a national prospective registry represents a strategic opportunity to lead the advancement of clinical cardiogenomics in Latin America.

The genetic diversity of the Mexican population provides a unique model for studying the interaction between genetic susceptibility and cardiometabolic exposure.[34]

The generation of evidence in this context will support the development of risk prediction models applicable across Latin American populations and foster regional collaboration networks.

CONCLUSIONS

This document represents the first multisociety consensus on precision cardiovascular medicine in Mexico, establishing a paradigm shift in cardiovascular prevention. The incorporation of Polygenic Risk Scores (PRS) moves risk assessment beyond conventional short-term estimation, enabling characterization of lifelong risk trajectories from birth and redefining the temporal framework of preventive cardiology.

In a population characterized by early cardiometabolic exposure and a high burden of premature cardiovascular events, identifying individuals with accelerated atherosclerotic progression has profound clinical, epidemiological, and economic implications. Within this context, PRS provides a novel opportunity to refine risk stratification and anticipate disease development, supporting earlier and more intensive preventive strategies.

The integration of genetic risk with traditional clinical models allows a more precise and individualized assessment of cardiovascular risk, particularly among individuals classified as having intermediate risk, where clinical uncertainty is greatest. However, current evidence supports its role as an adjunct rather than a replacement for established risk prediction tools.

Despite its promise, PRS implementation faces challenges, including lack of standardization, heterogeneity across populations, and underrepresentation of Latin American cohorts. These limitations highlight the need for cautious, evidence-driven, and context-specific adoption.

Accordingly, PRS should be implemented through a selective, stepwise approach linked to national evidence generation through the PRS-MX Registry. This strategy will enable real-world evaluation, model calibration, and optimization of healthcare resource allocation.

The collaboration among national societies positions Mexico as a regional leader in clinical cardiogenomics and establishes the foundation for locally validated risk models with broader applicability across Latin America.

Ultimately, the clinical value of PRS will depend on its validation in diverse populations, integration into clinical frameworks, and incorporation into scalable, cost-effective precision medicine strategies.

In this evolving landscape, polygenic risk is not merely a predictor of disease, it is a lens through which the future of cardiovascular prevention can be redefined.

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